

neck contracture, respiratory distress, micrognathia and infection.

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## Aicardi-Goutières syndrome: Phenotypic and genetic spectrum in a series of three cases<sup>☆</sup>



### Síndrome de Aicardi-Goutières: espectro fenotípico y genético en una serie de 3 casos

Dear Editor:

Aicardi-Goutières syndrome (AGS) is a rare hereditary disease whose exact prevalence is unknown. It was first described in 1984 by Jean Aicardi and Françoise Goutières as a progressive encephalopathy with onset in the first months of life characterised by cerebrospinal fluid (CSF) lymphocytosis and calcifications in the basal ganglia.<sup>1</sup> It manifests with irritability, psychomotor retardation, spasticity, dystonia, epileptic seizures, recurrent episodes of aseptic fever and microcephaly. The mortality is higher during the encephalopathic phase, and although the disease typically stabilises afterwards, it causes severe neurologic sequelae. Other characteristic features that may appear during its course are chilblains, ocular symptoms (mainly glaucoma), cardiac involvement or autoimmune disorders.<sup>2</sup> Type I interferons play a crucial role in the pathogenesis of AGS, in which their expression is upregulated leading to increased production.<sup>3</sup> For this reason, one of the classic laboratory findings in these patients is an elevated level of interferon alfa in CSF, along with pleocytosis and equally elevated levels of neopterin and biopterin. The potential usefulness of assessing the level of expression of interferon-

stimulated genes by interferon in peripheral blood as a marker is currently being investigated, as there is evidence that these levels stay high past the encephalopathic phase ("interferon signature").<sup>3–5</sup> Another key feature is the detection of neuroimaging abnormalities including calcifications in the basal ganglia and changes in the white matter (Fig. 1). To date, we know of 7 genes whose mutations can lead to upregulation of the interferon pathway: *ADAR*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *TREX1* and *IFIH1*. Heterozygous mutations have been described for the *TREX1*, *ADAR* and *IFIH1* genes, whereas the mutations reported in all other genes have been homozygous.<sup>2</sup> Mutations in the *IFIH1* gene were detected most recently (2014)<sup>4</sup> and are therefore the least frequent pathogenic variants, whereas mutations in the *RNASEH2B* and *TREX1* genes account for the highest proportion of diagnosed cases of AGS.

In the past few decades, thanks to advances in genetics allowing the detection of these specific mutations, evidence has emerged of a broad phenotypic spectrum beyond the classic presentation based on the causative gene. We present the cases of 3 patients given a diagnosis of AGS in the past 8 years with the aim of analysing their clinical features in relation to the underlying genetic defect (Table 1). In general, the presenting features of AGS were consistent with those described in the most recent case series in the literature: neonatal presentation (33%), microcephaly (66%), psychomotor retardation (100%), spasticity (100%), severe intellectual disability (66%) and calcifications on cranial CT (66%), although only one patient had epileptic seizures.

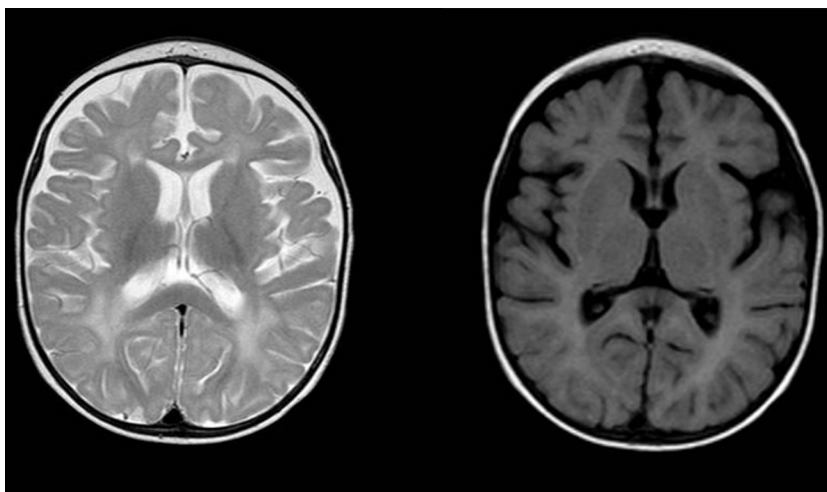
As noted before, homozygous mutations in the *RNASEH2B* gene are the most frequent variants that cause AGS and their phenotypic expression usually conforms the most to the classic presentation.<sup>4</sup> This was the case of the patient in our study that carried such a mutation, who had onset at age 10 months with irritability and psychomotor retardation and with characteristic neuroimaging and CSF findings.

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**Table 1** Characteristics of patients with Aicardi-Goutières syndrome.

	Case 1	Case 2	Case 3
<b>Genetics</b>	Homozygous mutation (p.Ala177Thr) in <i>RNASEH2B</i> gene	Homozygous mutation (341 G>A) in <i>TREX1</i> gene	Heterozygous mutation (c.992 C>G and p.Thr331Arg) in <i>IFIH1</i> gene
<b>Current age</b>	3 years	7 years and 4 months	12 years and 11 months
<b>Sex</b>	Male	Female	Male
<b>Origin</b>	Romania	Spain	Italy
<b>AP</b>	-	Week 36: intrauterine growth restriction Week 37: microcephaly, placental calcification	Cleft palate
<b>Clinical manifestations</b>			
Age at onset	10 months	Birth	2 years
Initial presentation	Irritability Psychomotor regression	Tremors, hypotonia, weak crying, growth failure	Motor skill delay
Psychomotor retardation	Yes	Yes	Yes
Language	2-Syllable words	No	Yes
Microcephaly	Yes	Yes	No
Chilblains	No	Yes	Yes
Epilepsy	No	Yes	No
Motor impairment	Spastic tetraplegia. GMFCS IV	Severe spastic tetraplegia. GMFCS V	Spastic tetraplegia. GMFCS IV
Movement disorder	No	Yes	No
Abnormal eye movements	No	No	No
Visual impairment	No	-	Myopia
Glaucoma	No	No	No
Hearing loss	-	-	No
Cardiac involvement	No	Mild tricuspid and mitral regurgitation	No
Recurrent fever	No	No	No
Intellectual disability	Yes	Yes, grave	Yes, mild
Other	-	-	Singleton-Merten syndrome: tooth abnormalities Axonal and demyelinating sensorimotor PNP
<b>CSF</b>			
CSF analysis	Increased protein	Pleocytosis and increased protein	-
Neopterin (nmol/L)	1.102 (12-55)	1.813 (12-55)	-
Biopterin (nmol/L)	66 (22-73)	53 (22-73)	-
INF alfa (IU/mL)	25 (<2)	75 (<2)	-
<b>Blood</b>			
<i>Interferon signature</i>	-	-	Gene overexpression
<b>Neuroimaging</b>			
Calcifications on CT	No	Yes. In basal and periventricular ganglia	Yes. Symmetrical calcifications in deep WM of frontal region and lentiform nucleus
Head MRI	Diffuse and patchy changes in WM intensity of both cerebral hemispheres, hyperintense on T2. Involvement of subcortical WM (sparing the U fibres) and periventricular WM	Generalised WM involvement with predominance of lobar WM including the subcortical U fibres of the frontal, temporal and occipital lobes, bilaterally and symmetrically, without cortical involvement	-

CSF, cerebrospinal fluid; CT, computed tomography; GMFCS, Gross Motor Function Classification System; INF, interferon; IUGR, intrauterine growth restriction; MRI, magnetic resonance imaging; PNP, polyneuropathy; WM, white matter.



**Figure 1** Diffuse and patchy signal abnormalities in white matter in both cerebral hemisphere, hyperintense in T2-weighted images. Enlarged subarachnoid space with frontotemporal predominance in both hemispheres, with widening of the interhemispheric fissure and increased ventricular size (in the absence of increased pressure), compatible with cortical and subcortical atrophy.

Twenty percent of cases of AGS may have a neonatal presentation, with the onset of disease occurring in utero.<sup>5</sup> Mutations in any of the 7 aforementioned genes may lead to this phenotype, but this early presentation is most frequently associated with the *TREX* gene.<sup>4,5</sup> The initial presentation of this form is similar to that of a TORCH infection, with hepatosplenomegaly, hypertransaminasaemia, thrombocytopenia and neurologic manifestations including extreme irritability, movement disorders and epileptic seizures.<sup>5</sup> These patients have a more severe course of disease and are at higher risk of death. The patient in our sample that presented with such a variant had a neonatal presentation and currently has the most severe form of illness of the 3.

Mutations in the *ADAR1* gene and especially the *IFIH1* gene are associated with a late onset of symptoms, after 1 year of life with normal psychomotor development.<sup>5</sup> In some of these cases, the syndrome has a benign course with relative preservation of language and motor skills. Our patient with a mutation in the *IFIH1* gene was a singular case in that he also had Singleton-Merten syndrome, a rare disease also caused by a mutation in the *IFIH1* gene and characterised by dental dysplasia, aortic calcifications and osteoporosis.<sup>6</sup>

Our aim is to underscore the significant phenotypic variability of AGS and its association with specific mutations for the purpose of both encouraging consideration of this diagnosis in cases with presentations that deviate from the classic form of disease and of contributing additional information on the course of disease and outcomes in these patients.

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